

Please cancel claims 2-4 and replace with new claims 6-7:

--6. A method of treating tumor growth and metastasis in a mammal comprising administering to said mammal a combination of: (i) a standard therapeutic dose of a COX2 inhibitor selected from the group consisting of celecoxib and rofecoxib, (ii) low dose aspirin in the amount of 70-85 mg, and (iii) antioxidant flavanoids, flavonoids or isoflavones.

7. A method of treating thromboembolic disorders in a mammal comprising administering to said mammal a combination of: (i) a standard therapeutic dose of a COX2 inhibitor selected from the group consisting of celecoxib and rofecoxib, (ii) low dose aspirin in the amount of 70-85 mg, and (iii) antioxidant flavanoids, flavonoids or isoflavones.--

### Remarks

Following entry of this Amendment Claims 1 and 5 will be amended, Claims 2-4 will be canceled and new Claims 6-7 will be added. A copy of the amended claims in clean form is attached as an appendix.

Claims 1 and 5 were amended to comply with claim formalities and to comply with 35 USC §112. New claims 6-7 replace canceled claims 2-3. Support for the amendments and claims can be found throughout the Specification.

### The Claim Objections

1. Claim 5 was objected for formalities; amendment to the claim moots this rejection.

### The §112 Rejections

Claims 1 and 4 were rejected under § 112 due to being unclear and vague; amendment to the claims moots this rejection.

### The §103(a) Rejections

Claims 1 and 4-5 were rejected under §103(a) in view of Lai et al. in view of Ares et al. or further in view of Anderson et al. Applicants note that they co-own and are co-inventors of the entire subject matter of the specification and as claimed.

Lai et al. teaches NSAIDS covalently linked to selective COX2 inhibitors and methods of use. Lai's contribution appears to be the development of pro-drug like compounds wherein NSAIDS and COX2 inhibitors are linked together and then become bioavailable following administration. Nowhere in Lai is it taught to administer, non-covalently linked, NSAIDS and COX2 inhibitors. Nor is it taught in Lai to administer NSAIDS in

low dose combination with a COX2 inhibitor. This is because Lai is concerned with single compounds covalently linked. Therefore, Lai could not and logically would not disclose, teach or suggest the combination administration of different doses of NSAIDS and COX2 inhibitors.

Ares et al. primarily teaches the use of flavones for gastrointestinal protection. Ares also teaches the combination therapy of NSAIDs and flavones, the theory being that flavones can protect the mucosal lining of the gastrointestinal surface against potential NSAID damage. Ares does not disclose, teach or suggest the combination therapy of COX2 inhibitors, low dose aspirin and flavanoids. In fact, Ares is not at all concerned with low dose aspirin, nor its combination with COX2 inhibitors. "Test Method II" is the only example in which Ares discloses the combination therapy of aspirin with a flavone (Column 10-11). In that example, a high dose of 100mg/kg acetasalicylic acid (aspirin) was used in combination with a flavone. This dose is much higher than Applicants' dose of 70-85 mg. Thus, Ares' teaching would actually lead one skilled in the art away from Applicants' invention.

Anderson et al. teach the use of the particular flavonoids, epigallocatechin-gallate and epicatechin gallate for the treatment of angiogenesis. Anderson does not teach on the combination of therapy of the particular flavonoids with aspirin or COX2 inhibitors. Therefore, there is nothing in Anderson that would motivate such a combination.

The Examiner states that it would have been obvious to incorporate the view of Ares with Lai. Such a combination, even if motivated by Ares, would yield a combination of a covalently linked NSAID-COX2 inhibitor compound with a flavone. This is not Applicants' invention. Applicants' methods do not involve these new compounds of Lai. Perhaps more importantly, such a combination still would not yield Applicants' combination of low dose aspirin in combination with a standard dose COX2 inhibitor and a flavanoid compound. Anderson does not add anything to this combination rejection of Applicants' invention. Anderson merely recites the use of specific flavonoids to treat angiogenesis.

The Examiner states in the alternative that the three references makes clear that COX2 inhibitors, aspirin and flavonoids have been individually used for treatment of inflammatory disorders and therefore, the "idea of combining them flows logically from their having been individually taught in the prior art." Applicants' respectfully request reconsideration. Lai teaches that therapy of the individual compounds is problematic and suggests the solution of covalently linking NSAIDS to COX2 inhibitors (see the Abstract and Columns 1-2). Ares teaches only the combination of NSAIDS with flavonoids, and such combination is only given in example at high doses of NSAIDS. Anderson merely teaches the use of specific flavonoids for treating angiogenesis. It is, therefore, respectfully submitted that the references do not provide any rational basis for motivating one skilled in the art to modify the teaching of the references to arrive at the combination therapy of Applicants'.

Reconsideration of this Section 103(a) rejection is therefore respectfully requested.

The claims are believed to be in condition for allowance and a notice to that effect is respectfully requested.

Respectfully submitted,

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